

- and their role in the activation of this enzyme by Gβγ subunits. *J. Biol. Chem.* **274**, 17152-17158 (1999).
6. Taylor, S.S. *et al.* Catalytic subunit of cyclic AMP-dependent protein kinase: structure and dynamics of the active site cleft. *Pharmacol. Ther.* **82**, 133-141 (1999).
- 5 7. Dhand, R. *et al.* PI3-kinase is a dual specificity enzyme - autoregulation by an intrinsic protein serine kinase activity. *EMBO J.* **13**, 522-533 (1994).
8. Stack, J.H. & Emr, S.D. Vps34p required for yeast vacuolar protein sorting is a multiple specificity kinase that exhibits both protein kinase and phosphatidylinositol-specific PI-3-kinase activities. *J. Biol. Chem.* **269**, 31552-31562
- 10 (1994).
9. Wymann, M.P. *et al.* Wortmannin inactivates phosphoinositide 3-kinase by covalent modification of Lys-802, a residue involved in the phosphate transfer reaction. *Mol. Cell. Biol.* **16**, 1722-1733 (1996).
10. Bondeva, T. *et al.* Bifurcation of lipid and protein kinase signals of PI3Kγ to
- 15 the protein kinases PKB and MAPK. *Science* **282**, 293-296 (1998).
11. Vanhaesebroeck, B. *et al.* Autophosphorylation of p110δ phosphoinositide 3-kinase: a new paradigm for the regulation of lipid kinases *in vitro* and *in vivo*. *EMBO J.* **18**, 1292-1302 (1999).
12. Kim, K. & Cole, P.A. Measurement of a Brønsted nucleophile coefficient and
- 20 insights into the transition state for a protein tyrosine kinase. *J. Am. Chem. Soc.* **119**, 11096-11097 (1997).
13. Marshall, C.J. Ras effectors. *Curr. Opin. Cell Biol.* **8**, 197-204 (1996).

14. Moodie, S.A. *et al.* Different structural requirements within the switch II region of the Ras protein for interactions with specific downstream targets. *Oncogene* **11**, 447-454 (1995).
15. Rodriguez-Viciana, P. *et al.* Role of phosphoinositide 3-OH kinase in cell transformation and control of the actin cytoskeleton by Ras. *Cell* **89**, 457-467 (1997).
16. Nassar, M. *et al.* The 2.2 Å crystal structure of the Ras-binding domain of the serine/threonine kinase c-Raf1 in complex with Rap1A and a GTP analogue. *Nature* **375**, 554-560 (1995).
17. Huang, L., Hofer, F., Martin, G.S. & Kim, S.-H. Structural basis for the interaction of Ras with RalGDS. *Nature Struct. Biol.* **5**, 422-426 (1998).
18. Essen, L.-O., Perisic, O., Lynch, D.E., Katan, M. & Williams, R.L. A ternary metal binding site in the C2 domain of phosphoinositide-specific phospholipase C- $\delta$ 1. *Biochemistry* **36**, 2753-2762 (1997).
19. Rao, V.D., Misra, S., Boronenkov, I.V., Anderson, R.A. & Hurley, J.H.
20. Structure of type II $\beta$  phosphatidylinositol phosphate kinase: a protein kinase fold flattened for interfacial phosphorylation. *Cell* **94**, 829-839 (1998).
20. Groves, M.R., Hanlon, N., Turowski, P., Hemmings, B.A. & Barford, D. The structure of the protein phosphatase 2A PR65/A subunit reveals the conformation of its 15 tandemly repeated HEAT motifs. *Cell* **96**, 99-110 (1999).
21. Vetter, I.R., Arndt, A., Kutay, U., Görlich, D. & Wittinghofer, A. Structural view of the Ran-importin  $\beta$  interaction at 2.3 Å resolution. *Cell* **97**, 635-646 (1999).
22. Dennis, P.B., Fumagalli, S. & Thomas, G. Target of rapamycin (TOR): balancing the opposing forces of protein synthesis and degradation. *Curr. Opinion Genet. Develop.* **9**, 49-54 (1999).

23. Leslie, A.G.W. Recent changes to the MOSFLM package for processing film and image plate data. in *Joint CCP4 and ESF-EACMB Newsletter on Protein Crystallography* Vol. 26 , Daresbury Laboratory, Warrington, UK, 1992).
24. CCP4. Collaborative Computing Project Number 4: A suite of programs for  
5 protein crystallography. in *Acta Crystallogr. D* Vol. 50 760-763 , 1994).
25. Terwilliger, T.C. & Berendzen, J. Automated structure solution for MIR and MAD. *Acta Crystallogr. D* **55**, 849-861 (1999).
26. de La Fortelle, E. & Bricogne, G. Maximum-likelihood heavy-atom parameter  
10 refinement for multiple isomorphous replacement and multiwavelength anomalous diffraction methods. *Methods Enzymol.* **276**, 472-494 (1997).
27. Jones, T.A., Zou, J.-Y., Cowan, S.W. & Kjeldgaard, M. Improved methods for building protein models in electron density maps and the location of errors in these models. *Acta Crystallogr. A* **47**, 110-119 (1991).
28. Brunger, A.T. *et al.* Crystallography & NMR system: A new software suite for  
15 macromolecular structure determination. *Acta Crystallogr. D* **54**, 905-921 (1998).
29. Nicholls, A., Sharp, K.A. & Honing, B. Protein folding and association: Insights from the interfacial and thermodynamic properties of hydrocarbons. *Proteins Struct. Funct. Genet.* **11**, 281-296 (1991).
30. Yamaguchi, H. & Hendrickson, W.A. Structural basis for the activation of  
20 human lymphocyte kinase Lck tyrosine phosphorylation. *Nature* **384**, 484-489 (1996).

The preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limiting the remainder of the disclosure in any way  
25 whatsoever. The entire disclosure of all applications, patents and publications, cited